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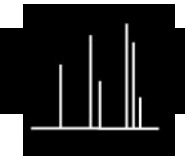
MASS SPECTROMETRY



Spectrometry–Mass Spectrometry Ion Mobility

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Introduction

The principle of mass spectrometry (MS) is the separation of ions in a vacuum, using an electrical or magnetic field or a combination of both. The ions may be formed through a variety of processes, but it is perhaps the fragmentation of the molecular ion that produces much of the analytical power of the technique. Mass-to-charge ratios are recorded and the structure of the parent ion may be determined from the ion molecular mass and the pattern of the fragment ions recorded. Experienced mass spectrometrists can recognize typical fragment ion patterns, however, although there are libraries available for the automated identification of mass spectra, careful judgement must be used in the final assignment of the compound's identity. The theory and uses of MS have been well documented as an analytical technique both as a standalone and a hyphenated technique, for example coupled with gas chromatography (GC-MS).

Less is known about the chemistry within ion mobility spectrometers, which are used in the field to monitor for contraband substances such as explosives, drugs, and on the battlefield to detect chemical warfare agents. Originally referred to as plasma chromatography, ion mobility spectrometry (IMS) is a technique concerned with the formation of ion-molecule clusters in air and their movement in an electric field, at or close to atmospheric pressure. The average ion velocity of an ion species in an electric field, v_d, is the product of that electric field, E, and a constant of proportionality, K, i.e. $v_d = KE$. K is called the mobility of the ions, and is characteristic of a particular ion species in a specified drift gas. K may be calculated indirectly from drift time, t_d, from the equation $t_d = l_d/v_d$, where l_d is the drift length. The theory of ion mobility and reaction chemistry is covered in two monographs listed in the Further Reading section, and need not be reproduced here. Notably, the Mason–Schamp equation for mobility (an equation that attempts to reconcile fundamental properties of ions with their mobility) includes a term containing a collision integral, to which mobility is inversely proportional. The value of the collision integral is determined by the cross-section. Therefore, the mobility, and consequently the ion drift velocity, is dependent upon mass, size, shape, and polarizability. The mobilities observed for ions are weighted averages of the mobilities of all the cluster ions participating in a localized equilibrium between the ion swarm and the neutral molecules they encounter as they traverse the drift region. If the drift gas, electric field gradient, temperature, pressure, and therefore the molecular number density remain constant, mobility depends only on ion charge, reduced mass, and collision cross-section. The collision processes undergone by ions during their drift time are very complicated, and are much too complicated to go into here. However, it must be noted that these processes are affected by variations in temperature and pressure in the drift region. Ion cluster formation and fragmentation are also governed by temperature. Therefore, to simplify the situation, and to allow easy comparison between different systems, mobility of an ion is normalized for temperature and pressure, the corrected term being referred to as reduced mobility, K_0 (μ_0 in some texts).

The initial distribution of ions immediately following ionization is modified by various chemical

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reactions, forming more stable ions. In clean air, these ions form what is called a reactant ion peak (RIP). Positive ion chemistry can involve proton transfer, nucleophilic attachment, hydride or hydroxide extraction, and oxidation; negative ion chemistry involves electron capture, charge transfer, dissociative capture, proton abstraction, and electrophilic attachment; both positive and negative chemistries can be subject to complex rearrangements.

When a sample atmosphere enters the ion mobility spectrometer, many competitive reactions occur and to a first approximation proton or electron affinities may define the reaction pathways. These competing species may be target or possible interference compounds. Ion mobility spectrometers respond to a broad range of compounds with various functional groups. Therefore, complicated spectra are common in ion-molecule systems based upon water chemistry, due to the relatively low proton affinity of the water molecule. Selectivity may be improved with the introduction of trace quantities of an appropriate dopant chemical into the detector carrier gas, thereby altering the degree of affinity required for reaction. This can have an effect on resolution, sensitivity, response and recovery times.

Whilst ion mobility spectrometers respond to many compounds, in the field the operator is only able to identify the compound being detected, by an ion mobility spectrometer, from its display. The efficacy of the instrument display depends upon calibration and software programming. However, as the observed peaks represent cluster ions participating in a localized equilibrium, even in the laboratory, with instrumentation capable of displaying the mobility spectra, the accurate identification of species may be difficult.

Although identification of unknowns by IMS alone is problematic, the coupling together of IMS and MS (IMS-MS) produces a powerful technique. The masses of ion-molecule clusters forming the RIP and product ion peaks are recorded either in positive or negative mode mass spectra, depending on the polarity of the ions being studied. When tuned ion analysis is performed on a specific mass in the mass spectrum, the mobility of the ion mass can be determined, i.e. its position in the mobility spectrum. With the technique enhanced, further by coupling IMS to tandem MS, the composition of ion-molecule clusters can be identified from the results of collision-induced dissociation (CID).

History

In the 1960s, Cohen (of the Franklin GNO Corporation) worked on the development of the ion mobility spectrometer, resulting in a US patent in 1971. The instruments were developed to generate information concerning negative ions produced from specific compounds in air under atmospheric pressure conditions. This early instrumentation was to have wider application for the analysis of ultra-trace quantities of many organic molecules forming either positive or negative ions. Cohen went on to form the company PCP, and to produce commercially available IMS-MS instrumentation.

By the early 1970s, Karasek was already employing IMS as part of a hyphenated technique, using IMS-MS to determine the identity of species separated through a GC. Even without the GC in-line, it was becoming evident that IMS-MS was a powerful identification technique.

In the late 1970s and the 1980s, IMS research was directed from fundamental studies to application research, with a view to solving specific analytical problems relating to the rapid detection of volatile organic compounds in the field. Specifically, IMS was the subject of military research programmes, designed to enhance the real-time detection of chemical warfare agents. IMS-MS still played an important role in understanding the ion-molecule chemistry, which was necessary to progress the development and reliability of the field deployable IMS instrumentation. A study of the ion-molecule behaviour of selected agents and interference compounds has been made by IMS-MS. IMS-MS has also been used to support some of the IMS programmes that have been applied to more general, as well as specific, monitoring requirements. Industrial applications have been directed towards monitoring for toxic chemicals, and chemicals considered to be hazardous to man or the environment. These include acid and stack gases (e.g. hydrogen fluoride), aliphatic and aromatic amines, ketones, isocyanates, halogens, solvents, ethers, anaesthetics, fuels, nicotine, polychlorinated biphenyls, mixtures of organic compounds, organophosphorus compounds, certain hydrocarbons (e.g. benzene), perfluoroisobutene, and volatile organic compounds used in the semiconductor industry. With social pressures for a greener environment, further IMS techniques are being developed, for example, for the identification of polymers, using laser ablation-IMS, to assist with sorting plastics for recycling. The need to detect pollutants in liquid media is becoming more desirable, e.g. the detection of aniline in hexane, and of aqueous ammonia in rivers, wastewaters and drinking water treatment facilities. This problem requires a means of separating the analyte from the liquid medium, usually in the form of a selectively permeable membrane. IMS analysis proceeds once the analyte has been transferred from the liquid to the

vapour phase. IMS has also been investigated for the detection of bacteria in water and wastewater sources, using pyrolysis before introduction.

Detection of explosives is a specific and very important area of contraband detection at trace levels: RDX, TNT, PETN, NG, EGDN, HMX, EGDN, 2,4-DNT, ammonium nitrate, and tetryl detection by IMS have all been investigated. Detection of illicit drugs by IMS is another important area, which has benefited from confirmation of detected species by IMS-MS analysis. Due to legal requirements for forensic and law enforcement purposes, alleged criminals charged with the clandestine manufacture of illegal drugs in the USA must be charged with the manufacture of specific drugs in order for the case to go to court; a blanket charge of clandestine drug manufacture is inadmissible. Drugs detected include heroin, cocaine, barbiturates, amphetamines, and LSD. Prescription drugs such as benzodiazepines are also detected by IMS. The pressure to be absolutely certain about the identity of target compounds emphasizes the advantages of powerful analytical techniques such as IMS-MS, which enhances the development and calibration of detection equipment.

A more specific application is of potential use to the forestry industry, which involves the identification of different timbers before processing. Fast thermolysis-IMS has proved successful for certain wood species. Wetwood, an abnormal condition of wood from both deciduous and coniferous trees caused by bacterial infection, was detected in Northern Red Oaks using this technique.

Although IMS-MS is necessarily a laboratory-based technique, it continues to play a very important part in the understanding of ion-molecule chemistry and the development of IMS equipment that, through user requirements, is becoming miniaturized. Hill continues to develop hyphenated IMS techniques, sometimes employing different ionization methods, including electrospray IMS-MS. The ion-molecule chemistry of different ionization techniques can be characterized readily by IMS-MS techniques. These fundamental studies have led the way for IMS-MS research into biomolecular sciences because, until the application of electrospray ionization, the biomolecules had been too large for successful ionization by more traditional methods employed for IMS. Clemner and Jarrold were able to further the research by determining the conformation of biomolecules by IMS.

A chronology of the history of IMS-MS is given in **Table 1**.

Table 1 History

1890s	Studies of the ionization of air
1897	Study of the velocity of positive rays in an electric field (Thomson & Rutherford)
1900s	Langevin studies of ionized air and mathematical/chemical models for ion mobilities
1907	First mass spectrometer
1919	Determination of atomic weights using MS
1946	Time of flight mass analyser
1953	Quadrupole MS
1960s	Drift tube mass spectrometers
1965	First IMS instruments (plasma chromatographs) were developed (Franklin GNO Corporation)
1966	Studies of chemical ionization
1967	Tandem MS
1968	Electrospray ionization for MS
1970s	Research led by Cohen and Karasek using both IMS and IMS-MS techniques
1971	First IMS patent issued in the USA (Cohen MJ, US patent 3,621,239)
1974	Atmospheric pressure ionization MS
1977	IMS-MS demonstration of ion-molecule behaviour of chemical warfare agents
1982	High field asymmetric waveform IMS-MS (FAIMS-MS)
1983	IMS-MS studies of reactant ion distributions in an ion mobility spectrometer with a membrane inlet system
1984	GC-IMS Corona discharge IMS
1985	IMS-MS identification of structurally different ions of the same mass
1986	IMS-MS analysis of prescription and illicit drugs
1987	Laser desorption IMS-MS
1990	IMS-MS used to study the site of protonation in anilines IMS-MS used in the semi-conductor industry to determine cleanliness
1992	IMS-MS analysis of marijuana vapours and cigarette smoke
1994	IMS-MS confirmation of ion-molecule clusters disclosed
1997	Development of ESI-high resolution IMS-MS (Washington State University) Development of ion-trap-IMS-TOFMS systems for the elucidation of biomolecular structures

An Ion Mobility Spectrometer–Mass Spectrometer

An ion mobility spectrometer consists of an ion-molecule reaction chamber, incorporating an ionization region, coupled to a drift region via a shutter grid. A schematic diagram is shown in **Figure 1**. The drift region contains a screen grid and an ion collector. A typical cell consists of metal guard rings, separated by insulators, connected to a resistance network with a high voltage attached to one end of the resistor chain, to produce a uniform electric field along the cell, usually of the order of a few hundred V cm^{-1}. Clean carrier gas is ionized by irradiation, usually with beta particles from a ^{63}Ni radioactive source, to form positive and negative reactant ions and consequently RIPs. The ion-molecule chemistry can be altered by the introduction of a dopant chemical at

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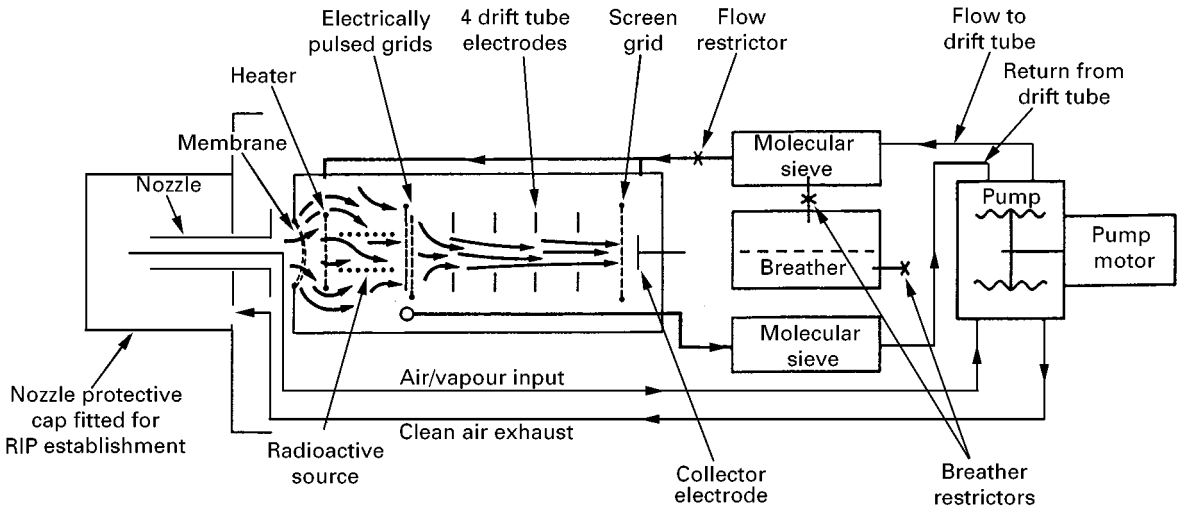

Figure 1 Schematic of an ion mobility spectrometer.

a controlled rate. Samples introduced into the ion mobility spectrometer may react to form product ions, the equilibrium concentrations of which are governed by proton affinity or electron affinity. If introduced into an electric field they will migrate according to their polarity and that of the applied field as, between collisions, individual ions have a component of acceleration in the direction of the applied field. Ions pass from the reaction region to the drift region via a shutter grid, which is pulsed open to allow a finite number of ions to enter the drift region. Operation of the shutter grid starts the timing sequence, which measures drift time. A counter-flow of clean drift gas enters the drift region near the collector electrode, which is shielded by a screen grid in order to prevent induced charge, which would lead to a distorted current peak. By monitoring the collector electrode from the instant the voltage pulse is applied to the grid, a mobility spectrum (see **Figure 2**) is generated. Mobility spectra can be generated continuously by repetitive pulsing of the grid. Typically, 25 ms is sufficient time to allow all ions to drift from the grid to the collector electrode. The signal-to-noise ratio is relatively noisy because only small ion currents are involved. The signal-to-noise ratio may be improved by averaging the signal over several scans.

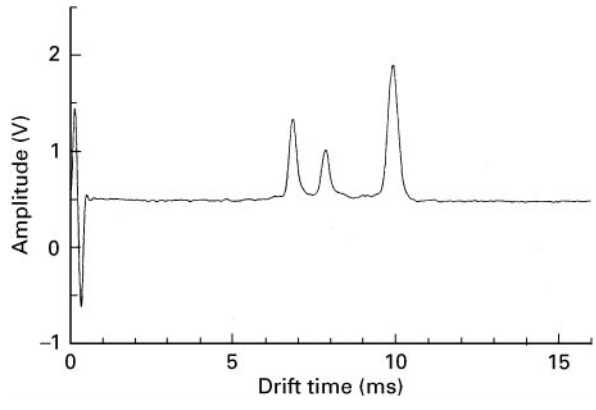

Figure 2 An ion mobility spectrum.

In a mass spectrometer, molecules are ionized by any one of a number of techniques. These ions are then analysed using either magnetic or electric fields or a combination of both and are separated according to their mass-to-charge ratio before being detected. In mass spectrometers using magnetic field separation, a repeller plate directs ions to a set of accelerator plates, used to produce a beam of rapidly moving ions, which are directed into a uniform beam by focussing slits. Neutral molecules are drawn off by vacuum pumps. In a quadrupole mass spectrometer, an oscillating electrostatic field is set up between four rods, two diagonally opposite rods having direct current voltage applied and the other two rods having radio frequency applied. Ions acquire an oscillation in the electrostatic field set up according to the ratio of the direct current to the radio frequency amplitude. Ions of the correct m/z value undergo a stable oscillation of constant amplitude and pass through the analyser to reach the detector. Other ions undergo unstable oscillation and the amplitude of the oscillation increases until the ions strike one of the rods.

Current IMS-MS Applications

APCI-MS enables ion chemistry at pressures used in typical IMS systems to be studied, but some issues remain regarding cluster formation in the interface region and this could influence the interfacing of IMS

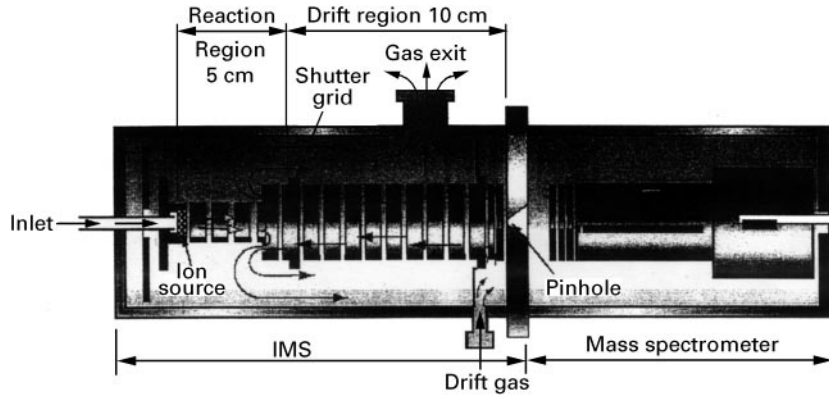

Figure 3 An ion mobility spectrometer–mass spectrometer.

(which operates close to atmospheric pressure) to MS. However, Spangler has recently published details regarding a better understanding of the behaviour at the IMS-MS interface.

An ion mobility spectrometer may be coupled to a mass spectrometer (see **Figure 3**) with sample transfer via a pinhole, typically 50 μ to 100 μ in diameter. The mass spectrometer used in conjunction with an ion mobility spectrometer enables m/z identification of the reactant and product ions. The mass spectrometer is initially programmed to scan through the chosen mass range with the IMS shutter grids continuously open. (If the ion mobility spectrometer is used in the normal pulsed mode it may take a very long time to obtain a mass spectrum, which may then not be representative.) Thus, it is possible to record ions created in an ion mobility spectrometer, and a mass spectrum of IMS sample ions is shown in **Figure 4**.

The mass spectrometer is then programmed to detect ions of one chosen mass. In this 'tuned' ion mode (with the IMS shutter grids operating normally), a drift spectrum of the selected ion species is generated (see **Figure 5**). Thus, it is possible to associate a particular ion mass with a particular ion mobility peak. Hence, IMS-tuned MS enables the reduced mobility for ions to be determined, but the signals are weak and a significant amount of data averaging is required. Because the signals are very low, mass spectrometers used in conjunction with ion mobility spectrometers are set to pulse counting mode. Sometimes the average of thousands of spectra is necessary to produce a mobility peak. Using IMS-quadrupole MS to determine the reduced mobilities of all the ion-molecule clusters in a mobility spectrum could take from several hours to days. IMS-TOF is much faster, because it is able to scan at 50 to 60 Hz about 1000 scans per mobility spectrum. Ewing and Stone have an IMS-tuned MS for investigating the kinetic thermodynamic relationship for the ion reactions.

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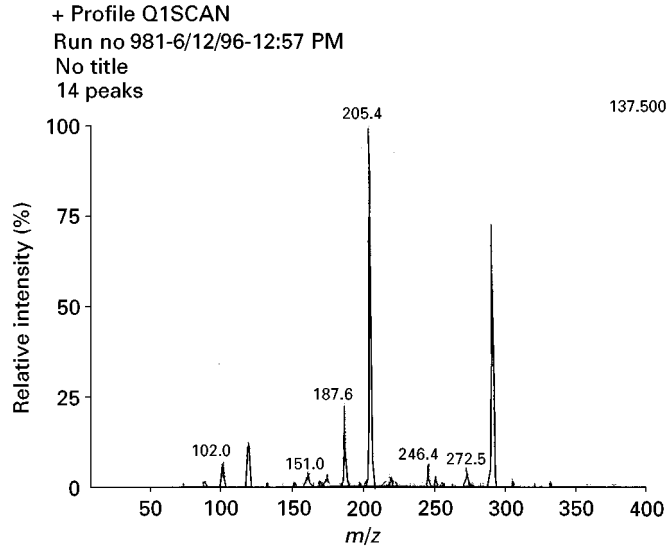

Figure 4 A mass spectrum of IMS sample ions.

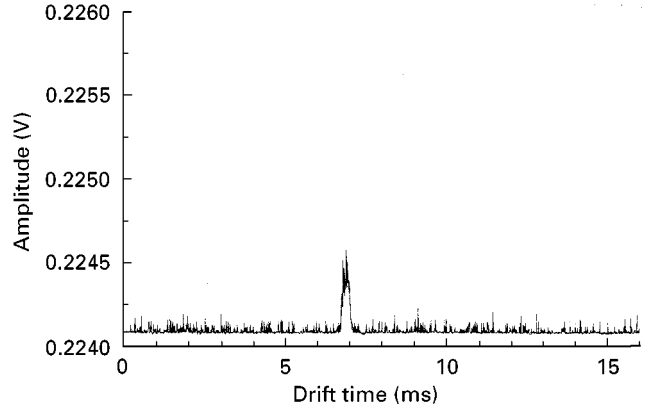

Figure 5 A drift spectrum of a selected ion species.

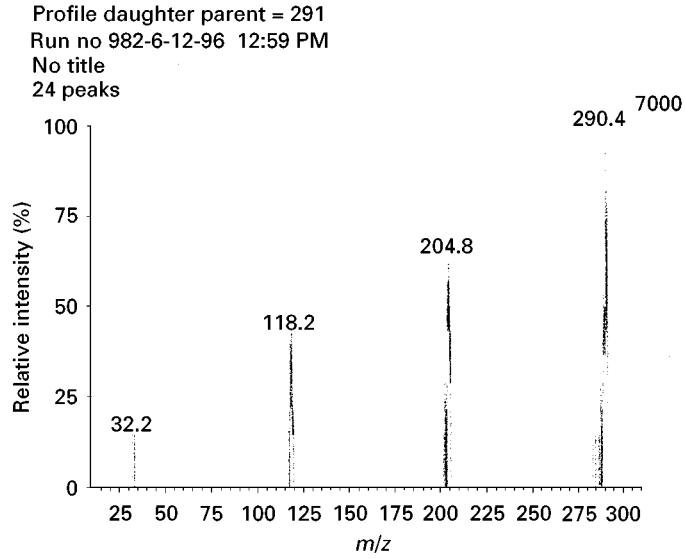

Figure 6 A mass spectrum of CID product ions.

IMS-MS-MS studies can be performed when IMS is coupled to a triple quadrupole mass spectrometer. An ion selected by the first quadrupole can be injected into a collision gas, for example argon, in a second quadrupole at 2×10^{-5} Torr (subjecting the cluster ions to CID), and then the product ions can be analysed in the third quadrupole. **Figure 6** shows a mass spectrum of CID product ions. Consequently, MS-MS analysis is used extensively in assigning ion identities. IMS coupled to triple quadrupole MS enables the composite identification of the ion-molecules found in a drift tube. However, the number of ions reaching the detector in IMS-MS-MS is extremely low and a large amount of averaging is required to determine structures.

See Colour Plate 46.

See also: **I/Mass Spectrometry. II/Chromatography: Gas:** Gas Chromatography-Mass Spectrometry. **III/Biomedical Applications:** Gas Chromatography-Mass Spectrometry; **Drugs and Metabolites:** Liquid Chromatography-Mass Spectrometry; **Explosives:** Gas Chromatography; Liquid Chromatography; Thin-Layer (Planar) Chromatography; **Forensic Toxicology: Thin-Layer (Planar) Chromatography; Forensic Sciences:** Capillary Electrophoresis; Liquid Chromatography; **Heroin: Liquid Chromatography and Capillary Electrophoresis.**

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